Original article

TITLE:

The use of aspirin for primary prevention of cardiovascular disease is associated with a lower likelihood of COVID-19 infection

RUNNING TITLE:

The advantages of aspirin for primary prevention for COVID19.

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Abbreviations:

SES – socioeconomic status;

COVID-19 – coronavirus SARS-Cov-2;

CVD - cardiovascular disease;

LHS - Leumit Health Services;

STING - stimulator of interferon genes.

Keywords: aspirin, COVID-19, Israeli cohort, disease likelihood

Conflicts of Interest: None.

Abstract

Acetylsalicylic acid (aspirin) is commonly used for primary and secondary prevention of cardiovascular diseases. Aspirin use is associated with better outcomes among COVID-19 positive patients. We hypothesized that aspirin use for primary cardiovascular disease prevention might have a protective effect on COVID-19 susceptibility and disease duration. We conducted a retrospective population-based cross-sectional study, utilizing data from the Leumit Health Services database. The proportion of patients treated with aspirin was significantly lower among the COVID-19-positive group, as compared to the COVID-19-negative group (73 (11.03 %) vs. 1548 (15.77%); p=0.001). Aspirin use was associated with lower likelihood of COVID-19 infection, as compared to non-users (adjusted OR 0.71 (95% CI, 0.52 to 0.99; p=0.041). Aspirin users were older (68.06 ± 12.79 vs. 56.63 ± 12.28 years of age; p<0.001), presented a lower BMI (28.77±5.4 vs. 30.37±4.55; p<0.0189) and showed higher prevalence of hypertension (56, 76.71%), diabetes (47, 64.38%) and COPD (11, 15.07%) than showed the aspirin non-users (151, 25.64%, p<0.001; 130, 22.07%, p<0.001; and 43, 7.3%, p=0.023, respectively). Moreover, COVID-19 disease duration (considered as the time between the first positive and second negative COVID-19 RT-PCR test results) among aspirin users was significantly shorter, as compared to aspirin non-users (19.8±7.8 vs. 21.9± 7.9 p= 0.045). Among hospitalized COVID-positive patients, a higher proportion of surviving subjects were treated with aspirin (20, 19.05%), as opposed to 1 dead subject (14.29%), although this difference was not significant (p=0.449). In conclusion, we observed inverse association between the likelihood of COVID-19 infection, disease duration and mortality and aspirin use for primary prevention.

Introduction

Surveillance of the clinical characteristics of patients with coronavirus disease 2019 (COVID-19) is important for clarifying the epidemiology of the disease. Several epidemiological studies have suggested that individuals with diabetes, cardiovascular disease (CVD), or chronic lung disease are at higher risk for COVID-19 infection (1,2). While many reports on COVID-19 have emphasized age-, sex- and comorbid disease-

related differences in health outcomes, pharmacological treatment differences in infection susceptibility have yet to be described in-depth.

Acetylsalicylic acid (aspirin) is among the most used medications in the world for the treatment of acute coronary syndromes and secondary prevention of CVD (3). Recent trials have, however, revealed that low-dose aspirin is not associated with significant differences in terms of primary CVD prevention (4,5). Therefore, the American College of Cardiology and the American Heart Association, who previously published guidelines for aspirin use in primary prevention, now discourage routine use of aspirin, particularly in patients with increased risk of bleeding (6). Nevertheless, many individuals still receive low-dose aspirin for primary prevention (7). Aspirin has multiple effects on different components of innate and adaptive immunity and, therefore, can influence susceptibility to viral infections (8). As such, we hypothesized that pre-existing treatment with low-dose aspirin might have a protective effect on COVID-19 susceptibility and disease duration among COVID-19-infected subjects. We accordingly analyzed the prevalence of low-dose aspirin therapy and clinical characteristics of that group in a large cohort of consecutive outpatients who tested positive in an RT-PCR assay designed to detect infection with COVID-19.

Results

Data sources

We directed a retrospective population-based cross-sectional study utilizing data from the Leumit Health Services (LHS) database. LHS is a nation-wide health maintenance organization in Israel, which provides services to some 725,000 members. LHS maintains a wide-ranging computerized database, continuously updated in terms of member hospitalizations and laboratory tests, demographics, medical diagnoses, and medical encounters. During each physician visit, the patient's diagnosis is entered or updated according to the International Classification of Diseases (9^{th} revision, ICD-9). At the same time, there is an ongoing process of validation by which the physicians are encouraged to report on patients, their diagnosis classification, medications and services. As such, the validity of diagnoses entered into the registry is high for important medical diagnoses, in particular those based on the LHS laboratory data (9-12).

The study period was from February 1, 2020 to June 30, 2020. The first COVID-19 patient in Israel was diagnosed in February 2020 and on July 9, the criteria used for defining recovery from COVID-19 were changed (13). All LHS enrollees who had been tested for COVID-19 during the study period were included in the present study. Testing for COVID-19 infection was performed upon physician referral, according to Israel Ministry of Health criteria for COVID-19 testing, which includes direct exposure to a confirmed COVID-19 patient and/or presentation of symptoms suggesting COVID-19 (essentially, a cough, shortness of breath or any other respiratory symptom, with fever). Nasopharyngeal swabs were taken and examined for COVID-19 by real-time RT-PCR performed with internal positive and negative controls, according to World Health Organization guidelines. The Allplex 2019-nCoV assay (Seegene, Seoul, Korea) was used until March 10, 2020, after which time the COBAS SARS-Cov-2 6800/8800 assay (Roche Pharmaceuticals, Basel, Switzerland) was employed. The study protocol was approved by the statutory clinical ethics committees of LHS and the Shamir Medical Center Institutional Review Board (Helsinki Committee approval #0129-20-LEU, Shamir Medical Center) on human research.

Study subjects

Data on demographics, laboratory results, and ICD-9 codes were derived from the LHS electronic medical records (EMR) system. COVID-19 RT-PCR testing of samples derived from nasopharyngeal swabs was performed by experienced personnel in a single centralized laboratory accordingly to international guidelines (14). All consecutive patients aged ≥40 years who had been tested for COVID-19 during the study period were included in the study. The EMR of each subject was reviewed and those patients receiving low-dose aspirin treatment 4 weeks prior to COVID-19 RT-PCR testing were identified. Individuals who had been diagnosed with coronary artery disease, cerebrovascular disease and/or peripheral vascular disease were classified as taking aspirin for secondary prevention and excluded from the study. Such exclusion was performed to reduce the risk of bias due to differences in social activity and hence differences in potential COVID-19 exposure between healthy and more socially active populations and those patients suffering from cardiovascular diseases and accordingly, less socially active.

Whole sample analysis from COVID-19-positive versus COVID-19-negative patients

A total of 10,477 subjects were identified who had been tested for COVID-19 by RT-PCR and who had received and purchased at least 3 prescriptions for aspirin for primary prevention. Comparison of various demographic and clinical characteristics in these subjects, both positive and negative for COVID-19, are presented in Table 1. As compared to the COVID-19-negative group, the COVID-19-positive group was slightly younger (57.89 ± 13.83 years vs. 59.11 ± 14.53 years; p=0.047) and included higher proportions of males (375 (56.65%) vs. 4307 (43.88%); p<0.001) and persons from low-medium socioeconomic status (SES) (506 (76.44%) vs. 5828 (59.38%); p<0.001), presented a higher BMI (28.96 ± 5.29 kg/m^2 vs. 28.35 ± 5.61 kg/m^2; p=0.012) and contained a significantly lower proportion of smokers (37 (7.3%) vs. 1806 (23.35%); p<0.001). The prevalence of arterial hypertension (207 (31.27%)) and COPD (1170 (11.92%)) were higher in the COVID-19-negative group than in the COVID-19-positive group (3719 (37.89%); p<0.001 and 54 (8.16%); p=0.003, respectively). In contrast, the prevalence of obesity was higher in the COVID-19-positive group (232 (40.56%) vs. 2871 (34.3%); p=0.002). The prevalence of diabetes was similar in both groups. The proportion of patients treated with aspirin or statins was significantly lower among the COVID-19-positive group, as compared to the COVID-19-negative group (73 (11.03 %) vs. 1548 (15.77%); p=0.001, and 108 (16.31 %) vs 2198 (22.43 %); p=0.003, respectively). Those subjects who had purchased at least 3 prescriptions for aspirin and statins were less associated with the likelihood of COVID-19 infection than were those who did not (adjusted OR 0.71 (95% CI, 0.52 to 0.99; p=0.041) and adjusted OR 0.70 (95% CI, 0.53-0.92; p=0.012)) (Table 1). Moreover, there were no differences between COVID-19-positive and COVID-19-negative subjects in terms of the proportion of patients treated with ACE inhibitors (65 (9.82 %) vs.1162 (11.86 %)) and angiotensin II receptor blockers (ARBs) (28(4.23 %) vs. 540 (5.51 %))(Table 1).

Demographic and clinical characteristics of COVID-19-positive subjects receiving aspirin treatment (aspirin users) vs. COVID-19-positive subjects not receiving aspirin treatment (aspirin non-users) are presented in Table 2. Aspirin users were older (68.06 ± 12.79 vs. 56.63 ± 12.28 years of age; p<0.001), presented a lower BMI (28.77±5.4 vs. 30.37±4.55; p<0.0189) and showed higher prevalence of hypertension (56 (76.71%)),

diabetes (47(64.38%)) and COPD (11 (15.07 %)) versus aspirin non-users (151 (25.64%), p<0.001; 130 (22.07%), p<0.001; and 43 (7.3%), p=0.023, respectively). Moreover, among aspirin users, a significantly higher proportion of subjects were treated with ACE inhibitors (25 (34.25 %)), ARBs (10 (13.70 %)) and statins (52 (71.23 %)), relative to aspirin non-users (40 (6.79 %), p<0.001; 18 (3.06 %), p<0.001; and 56 (9.51 %), p<0.001, respectively). The variance inflation factor (VIF) was used to account for the problem of multi-collinearity among independent variables used. All VIFs were less than 5, indicative of a degree of multi-collinearity in our data, although one not sufficiently severe to warrant further corrective measures (see Table 1 and Figure 1).

Analysis of hospitalized versus community-treated COVID-19-positive patients

Demographic and clinical characteristics of hospital-treated COVID-19-positive patients (n= 112) vs. community-treated COVID-19-positive patients (n= 550) are presented in Table 3. Hospitalized patients were significantly older (62.89±12.19 vs. 56.91±12.19 years of age; p<0.001) and showed higher prevalence of hypertension (46 (41.07%)), diabetes (47 (41.96%)) and COPD (15 (13.39)) than did community-treated patients (161 (29.27)), p=0.014; (130 (22.07%)), p<0.001; and (39 (7.09)), p=0.026, respectively). Hospitalized patients also had significantly higher hemoglobin A1C levels than did community-treated patients (6.26%±1.85 and 5.70%±1.4, p=0.002, respectively). Older age and higher ages of comorbidities were noted among hospital-treated patients, as compared to community-treated patients. This may be explained by the significantly higher proportion of subjects treated with aspirin (21 (18.75%) versus 51 (9.27%), p= 0.003). After adjustment for age, sex and comorbidities, this difference disappeared (adjusted OR 1.00 (95% CI, 0.47-2.57; p=0.826)) (Table 3).

Seven subjects of the 112 hospitalized COVID-19-positive patients died during the study period. Their demographic and clinical characteristics are presented in Table 4. Dead subjects were significantly older (80.71±20.51 vs. 61.72±13.50 years of age; p<0.0007). After adjustment for other variables, only age, as a continuous variable, appeared to be a significant risk factor for mortality, introducing an additional 9% for every year (adjusted OR 1.09 (95% CI, 1.02-1.17; p=0.009)) (Table 4). Among surviving hospitalized patients, a higher proportion of subjects were treated with aspirin (20 (19.05%) vs. 1 (14.29%), adjusted OR 0.36 (95% CI, 0.02-6.85)) and statins (23 (21.90)

vs. 1 (14.29), OR 0.31 (95% CI, 0.01-6.57)), although this difference was not significant (p=0.449 and p= 0.514, respectively) (Table 4).

Conversion time of SARS-CoV-2 PCR test results from positive to negative among COVID-positive patients

To strengthen the hypothesis that aspirin pharmacotherapy for primary prevention has a possible protective effect against COVID-19 infection, a separate analysis of the conversion time of a SARS-CoV-2 RT PCR test result from positive to negative among COVID-19-positive subjects was performed. Demographic and clinical characteristics of COVID-19-positive patients with and without aspirin treatment are presented in Table 2. The time between the first positive SARS-CoV-2 RT-PCR test result and the first and second negative SARS-CoV-2 RT-PCR test results among aspirin users was significantly shorter, as compared to that time measured for aspirin non-users ((15.66±7.15 vs. 18.38± 7.71 days p= 0.0052) and (19.81±7.77vs. 21.91± 7.88 p= 0.045), respectively) (Table 2). Figure 2 presents the effect of aspirin on conversion time among COVID-19-positive patients, using a statistical R function Welch two-sample t-test. This means that a significant difference exists in all tests, with a significance threshold of p-value<0.05. These results indicate a reduction in the duration of illness by an average of about 1.2 times in the case of those taking aspirin.

Discussion

A large, nation-wide study revealed that the use of aspirin is associated with a decreased likelihood of a positive COVID-19 test result. Indeed, aspirin gained remarkable popularity during the 1918 Spanish Influenza pandemic, several decades prior to confirmation of its action on several components of innate immunity (8) and the *in vitro* efficacy against RNA viruses of the respiratory tract (18). The basic mechanism of the anti-viral activity of aspirin against RNA viruses relies on several biochemical and immunological pathways. Host response and clearance of viral infections heavily depend on the expression of type I interferon (IFN), which modulates cell responses and reprograms cells into an “anti-viral state” (19). RNA viruses, such as SARS-CoV and MERS-CoV, can escape immune system recognition via suppression of type I IFN signaling through an inhibition of STAT

family transcription factor phosphorylation (20). Another specific mechanism used by RNA viruses to evade host anti-viral responses involves up-regulation of prostaglandin E_2 (PGE_2) levels, which leads to an inhibition of type I IFN production and apoptosis in macrophages, thereby causing increased viral replication (21). As low-dose aspirin inhibits PGE_2 biosynthesis (22), this mechanism might enhance anti-viral immunity via induction of type I INF (23).

COVID-19 uses the transmembrane angiotensin-converting enzyme 2 (ACE2) as the host transmembrane cellular receptor for cell infection (24). Higher ACE2 expression may be of benefit in preventing COVID-19 infection, as COVID-19 virus particles may compete with angiotensin-2 protein for cell surface binding sites and cellular uptake (25). In addition, the stimulator of interferon genes (STING) induces type I INF production when cells are infected with DNA and RNA viruses (26). Furthermore, polymorphisms in the STING pathway contribute to the pathogenesis of COVID-19 infection (27). Interestingly, aspirin has been found to directly affect an acetylate cyclic GMP-AMP synthase (cGAS) that activates a type I INF response via the STING pathway (29). In COVID-19, excessive angiotensin II signaling due to poor ACE2-mediated conversion of angiotensin II at the cell surface could activate the STING pathway (30). Accordingly**,** Chow et al. suggested that COVID severity would be reduced among aspirin users. In their recent retrospective on an observational cohort study of adult patients admitted with COVID-19 to multiple hospitals in the United States, these authors found that aspirin use was associated with decreased rates of mechanical ventilation, ICU admission, and in-hospital mortality (28).

The present study sought to better understand the potential favorable effects of aspirin in aiding the human immune system battle COVID-19. At the same time, several studies have revealed that platelets can associate with SARS-Cov-2 RNA and are activated in response to COVID-19 infection (31-33). Recently, Zhang et al. demonstrated the expression of ACE2 and TMPRSS2 (Transmembrane Serine Protease 2 protein), which facilitates entry of viruses into host cells by proteolytically cleaving and activating viral envelope glycoproteins (34). SARS-CoV-2 can bind CD147 and CD26 in an ACE2-independent manner to interact with platelets (35, 36). Further studies are, however, needed to determine whether aspirin can disturb interactions of SARS-CoV-2 with targets on platelets, thereby delaying viral infection and propagation.

The present study, to our knowledge, is the first to examine the relationship between low-dose aspirin treatment and the likelihood of COVID-19 infection among a large cohort of outpatients listed in a nation-wide database. In addition, we found a reduction in COVID19 likelihood for individuals using both aspirin and statins (Figure 3). A major limitation in our observational study is the lack of control over treatments given to the study population. Unlike random assignment in clinical trials, where groups differ only in terms of treatment intervention, the treatment groups in observational studies, such as the present study, are likely to differ with respect to treatment intervention and other variables that can independently affect outcome. To avoid bias due to comparison of a healthy, more socially active population with patients suffering from severe cardiovascular comorbidity, we excluded all subjects taking aspirin for secondary prevention. We also applied multivariate logistic regression analysis adjusted for sex, age, smoking status, socioeconomic status (SES), chronic medication administration, laboratory data and comorbidities and used the variance inflation factor (VIF) (17) to check for multi-collinearity among independent variables. Another serious limitation is related to the observed shortening of PCR positivity among aspirin users, given how PCR testing was not performed on a daily basis in the community setting. However, two consecutive negative SARS-CoV-2 RT-PCR test results were recommended as a criterion for discharge and termination of social isolation by health authorities in different countries and were used for making a clinical decision regarding COVID-19 management (37). The shortening of the time needed for conversion of SARS-CoV-2 PCR test results from positive to negative observed here could reflect a resolution of symptoms (38) and have significant impact on COVID-19 patients. Another limitation is related to the different COVID-19 testing methods used in our cohort, given how the true sensitivity of testing remains unknown. Such limitation is typical of most similar epidemiological studies of COVID-19 infection.

Currently, aspirin is proposed for use as an anti-thrombotic drug for treating COVID-19 in patients with established hyper-coagulability (37). The RECOVERY II (Randomized Evaluation of COVID-19 Therapy II) trial, a randomized clinical trial, is now being planned to test the effectiveness of low-dose aspirin as an anti-inflammatory and anti-thrombotic treatment in COVID-19 patients (39, 40).

In conclusion, we observed inverse association between the likelihood of COVID-19 infection and aspirin use for primary prevention. Our data on the possible use of low-doses of aspirin for the prevention of COVID-19 infection are preliminary, yet intriguing. We thus need prompt clinical consideration of this safe, low-cost drug with the potential to favorably alter COVID-19 infection outcome. Such an effect would also provide immediate socio-economical relief by reduction of COVID-19 susceptibility. Therefore, our observations justify efforts to repeat this study using larger samples, including patients from other institutions.

Methods

Definitions

Medication use was deemed if the patient had been prescribed and had purchased at least 3 prescriptions of certain groups of medications, defined according to their Anatomical Therapeutic Chemical (ATC) codes, namely, aspirin (acetylsalicylic acid; ATC code B01AC06), Angiotensin-converting enzyme inhibitors (ACEI**;** ATC code C09A and C09B), Angiotensin II receptor blockers (ARB; ATC- code C09C and C09D) and lipid-lowering medications (statins; ATC code C10A), during the past twelve months. The period of disease duration was defined as the number of days between conversion of the first positive SARS-CoV-2 RT-PCR test result to the first two consecutive negative SARS-CoV-2 RT-PCR results (sampled at least 24 hours apart), according to Israel Ministry of Health guidelines (15, 16).

SES data were organized according to the Israel Central Bureau of Statistics classification system that includes 20 sub-groups, delineated according to home address. Classifications one to nine are considered low-medium SES, while classifications 10-20 are considered upper medium-high SES. Smoking status was defined based upon last electronic medical record (EMR) documentation made by the family physician. Rates of missing data were generally similar for COVID-19-positive and COVID-19-negative subjects. Levels of missing BMI and laboratory data were less than 10%. The greatest amount of missing data addressed smoking status (23% of adherent and 25% of non-adherent subjects).

Statistical analysis

Differences in demographic and clinical characteristics between subjects with negative and positive COVID-19 RT-PCR test results were analyzed using Student's t-test and Fisher's exact $\chi 2$ test for continuous and categorical variables, respectively, based on normal distribution and variable characteristics. Categorical data are presented as counts and percentages. Data on continuous variables with normal distribution are presented as means and standard deviation (SD). We applied multiple imputations for missing data under the assumption that data were missing at random, conditional on the observed data. Any problem of multi-collinearity among variables in the models was tested by calculating the VIF (17). Multiple regression analyses adjusted for sex, age, smoking status, comorbidity and chronic medication use served to estimate the odds ratios (OR) and 95% confidence interval (CI) for the independent association between aspirin treatment and COVID-19 RT-PCR test results. All statistical analyses were conducted using STATA 12 statistical package software (StataCorp, College Station, TX). R functions (Shapiro–Wilk and Welch two-sample t-test) were used for statistical assessment of disease duration figures. Visualizations relied on open source programs (Perl, R, GIMP, Inkscape). The Ggplot2 R package (Hadley Wickham, Garrett Grolemund R for Data Science, O'Reilly Media, 2017) was used to produce figures, including scatter plots, area charts, bar charts and 3D charts. Plots were prepared using in-house scripts written by the Frenkel-Morgenstern group in R and Perl.

Formulae for calculating the density of aspirin and statins

$N = \{patient_1, patient_2, ..., patient_{10460}\}$ is a set of the patients;

$Aspirin = \{yes, no\}$ is a set of the aspirin levels;

$Statins = \{yes, no\}$ is a set of the statin levels;

$AS = \{(Aspirin.yes \vee Statins.yes), (Aspirin.no \wedge Statins.no)\}$ is a set of the aspirin and statin levels;

$Age = \{40-45, 45-50, 50-60, 60-75, 75-85, 85+\}$ is a set of age levels (bins);

$Covid = \{yes, no\}$is a set of positive and negative COVID-19 patients;

$Drugs = \{Aspirin, AS\}$is a set of drugs used;

$$DAC = \{patient \in N : Drugs(patient) \wedge Age(patient) \wedge Covid(patient)\} \forall Drugs$$

$$densityDrugs = DAC \vee \frac{}{\{patient \in N : Covid(patient)\} \vee \cdot \frac{ageRange_{total}}{ageRange_{bin}} \cdot 100, \forall Drugs \wedge Age \wedge Covid}$$

$$\Delta densityDrugs = Covid.yes(densityDrugs) - Covid.no(densityDrugs), \forall Drugs \wedge Age$$

Author Contributions

EM, El.M have designed the study, EM, IG, SV, AGC, MFM, El.M have analyzed the data, AG and MFM have produced figures, EM has supervised the study, all authors have written the manuscript.

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Figure Legends

Figure 1: Three peak age groups at high-risk for contracting COVID-19: 45-50, 50-60, and 60-75 years old (red bars). These three age groups were included in the subsets Aspirin (A) and Aspirin & Statins (B) (the area highlighted in light blue). In the subsets of persons not treated with drugs, the age range of 40–45 years peaked (shown in the area highlighted in light pink). The delta density of the drugs was calculated by the formulae described in Methods.

Figure 2: Effects of aspirin on conversion time of SARS-CoV-2 RT PCR test results among COVID-19-positive patients. The p-values have been calculated by the standard t-test.

Figure 3: The frequency distributions (12 age groups ranging from 40 to 95+ years, in 5-year steps) of COVID-19-positive patients (top area) and corresponding negative patients (bottom area), who took aspirin and statins (highlighted in red) and who did not take these drugs (highlighted in light green).

Table 1. Demographic and Clinical Characteristics of Patients tested for COVID-19

	COVID-19-positive, n= 662	**COVID-19-negative, n= 9815**	**p-value**	**Multiple logistic regression model adjusted for sex and age OR (95% CI)**	**Multiple logistic regression model adjusted for sex, age, smoking, medication use and comorbidities* OR (95% CI)**	**VIF when all covariates are in the model**
Age, years (mean ± SD)	57.89 ± 12.83	59.11 ± 14.53	0.037	0.99 (0.99 - 1.00); p=0.778	1.01 (0.99 - 1.02); p=0.063	1.01
Sex (male), n (%)	375 (56.65%)	4307 (43.88%)	<0.001	1.70 (1.45 - 1.99); p<0.001	2.06 (1.57 - 2.69); p<0.001	1.02
Low-medium SES, n (%)	506 (76.44%)	5828 (59.38%)	<0.001	2.16 (1.79 - 2.60); p<0.001	1.80 (1.41 - 2.31): p<0.001	1.08
BMI, kg/m^2 (mean ± SD)	28.96 ± 5.29	28.35 ± 5.61	0.012	1.02 (1.01 - 1.03); p=0.005	1.01 (0.99 - 1.03); p=0.136	1.03
Current smoking, n (%)	37 (7.3%)	1806 (23.35%)	<0.001	0.23 (0.16 - 0.32); p<0.001	0.24 (0.16 - 0.37); p<0.001	1.73
Comorbidity						
Hypertension, n (%)	207 (31.27%)	3719 (37.89%)	0.001	0.75 (0.62 - 0.91); p=0.004	0.77 (0.59 - 0.99); p=0.048	1.91
Diabetes mellitus, n (%)	177 (26.74%)	2752 (28.04%)	0.468	0.97 (0.80 - 1.17); p=0.739	0.81 (0.60 - 1.07); p=0.128	1.73
COPD, n (%)	54 (8.16%)	1170 (11.92%)	0.003	0.65 (0.49 - 0.87); p=0.004	0.66 (0.45 - 0.96); p=0.030	1.69
Obesity, n (%)	232 (35.04%)	2871 (28.33%)	0.002	1.27 (0.99 - 1.64); p=0.079	1.21 (0.98 - 1.51); p=0.067	1.85
Laboratory data						
HgbA1C % (mean ± SD)	5.71 ± 1.52	5.59 ± 1.42	0.005	1.08 (1.02 - 1.15): p=0.012	1.10 (1.00 - 1.21); p=0.049	1.07
Total cholesterol (mean ± SD)	192.91 ± 40.93	197.14 ± 44.83	0.021	0.99 (0.99 - 1.00); p=0.101	0.99 (0.98 - 1.00); p=0.506	2.67
LDL cholesterol (mean ± SD)	117.71 ± 36.68	120.27 ± 39.54	0.114	0.99 (0.99 - 1.00); p=0.259	1.00 (0.99 - 1.01); p=0.659	2.21
HDL cholesterol (mean ± SD)	47.29 ± 12.11	48.83 ± 13.42	0.005	0.99 (0.99 - 1.00); p=0.648	1.01 (0.99 - 1.02); p=0.312	1.01
Triglycerides (mean ± SD)	136.38 ± 84.92	134.71 ± 85.97	0.649	0.99 (0.99 - 1.00); p=0.669	0.99 (0.99 - 1.00); p=0.853	1.03
Medications						
Aspirin, n (%)	73 (11.03 %)	1548 (15.77%)	0.001	0.63 (0.46 - 0.86); p=0.004	0.71(0.51; 0.99); p=0.041	3.82
ACE inhibitors	65 (9.82 %)	1162 (11.86 %)	0.161	0.81 (0.62 - 1.07); p=0.134	1.04 (0.75 - 1.46); p=0.809	2.03

ARB's	28 (4.23 %)	540 (5.51 %)	0.183	0.78 (0.53 -1.15); p=0.214	0.89 (0.56 - 1.39); p=0.610	2.44
Statins	108 (16.31 %)	2198 (22.43 %)	0.003	0.67 (0.54 - 0.83); p<0.001	0.70 (0.53 - 0.92); p=0.012	3.56

Table 2. Demographic and clinical characteristics of Coved-19 positive patients with and without aspirin

	COVID-19 positive subjects with Aspirin **n= 73**	**COVID-19 positive subjects without Aspirin** **n= 589**	**p-value**
Age, years (mean ± SD)	68.06 ± 12.79	56.63 ± 12.28	<0.001
Sex (male), n (%)	43 (58.90 %)	332 (56.37 %)	0.848
Low-medium SES, n (%)	50 (68.49 %)	456 (77.42 %)	0.511
BMI, kg/m^2 (mean ± SD)	28.77±5.4	30.37±4.55	0.0189
Current smoking, n (%)	2 (2.74 %)	35 (5.94 %)	0.278
Comorbidity			
Hypertension, n (%)	56(76.71%)	151(25.64%)	<0.001
Diabetes mellitus, n (%)	47(64.38%)	130(22.07%)	<0.001
COPD, n (%)	11 (15.07 %)	43 (7.30 %)	0.023
Obesity, n (%)	34 (46.58 %)	198 (33.62 %)	0.059
Laboratory data			
HgbA1C % (mean ± SD)	6.64 ± 1.62	5.63 ± 1.46	< 0.001
Total cholesterol (mean ± SD)	176.89 ± 46.31	195.04 ± 39.73	0.0004
LDL cholesterol (mean ± SD)	102.91 ± 40.27	119.69 ± 35.76	< 0.001
HDL cholesterol (mean ± SD)	44.49 ± 11.07	47.66 ± 12.19	0.035
Triglycerides (mean ± SD)	146.34 ± 70.21	135.06 ± 86.67	0.286
Medications			
ACE inhibitors	25 (34.25 %)	40 (6.79 %)	< 0.001
ARB's	10 (13.70 %)	18 (3.06 %)	< 0.001

Statins	52 (71.23 %)	56 (9.51 %)	< 0.001
Time from 1st positive SARS-CoV-2 RT-PCR test result to 1st negative SARS-CoV-2 RT-PCR test result, days (mean ± SD)	15.66±7.15	18.38±7.71	0.0052
Time from 1st positive SARS-CoV-2 RT-PCR test result to 2nd negative SARS-CoV-2 RT-PCR test result, days (mean ± SD)	19.81±7.77	21.91± 7.88	0.045

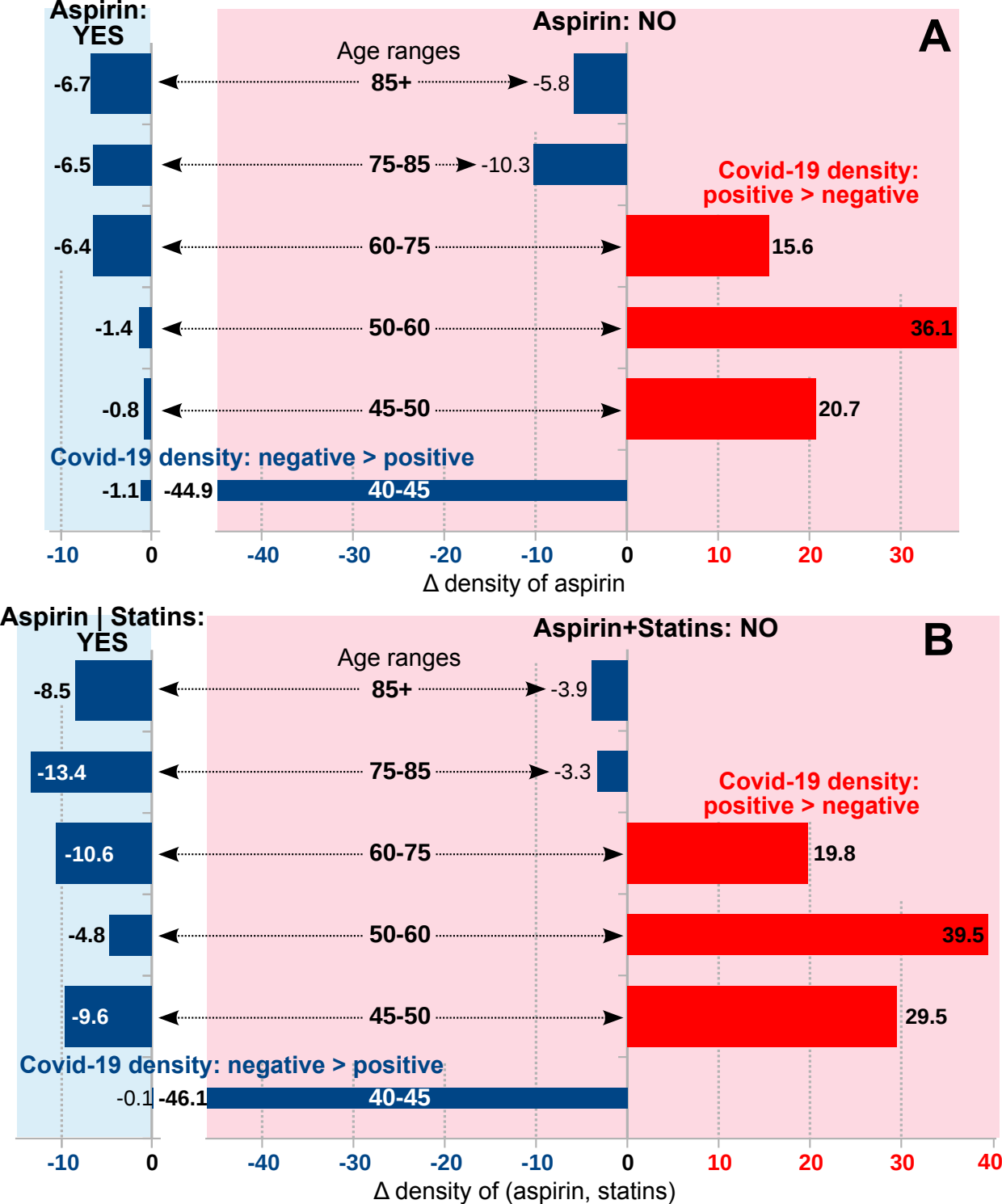
	Hospital-treated COVID-19-positive patients n= 112	**Community - treated COVID-19-positive patients n= 550**	**p-value**	**Multiple logistic regression model adjusted for sex and age OR (95% CI)**	**Multiple logistic regression model adjusted for sex, age, smoking status, medication use and comorbidities*, OR (95% CI)**
Age, years (mean ± SD)	62.89 ±14.67	56.91±12.18	<0.001	1.03 (1.01-1.04); p<0.001	1.02(1.00-1.05); p=0.016
Sex (male), n (%)	62 (55.36%)	313 (56.9%)	0.762	92 (0.61-1.40); p=0.73	0.70(0.38-1.05); p=0.263
Low-medium SES, n (%)	80 (71.43%)	426 (77.45%)	0.170	0.77(0.48-1.23); p=0.278	0.69(0.37-1.29); p=0.243
BMI, kg/m^2 (mean ± SD)	29.05±6.16	28.94±5.1	0.860	1.00(0.96-1.04); p=0.84	0.92(0.84-1.01); p=0.088
Currently smoking, n (%)	6 (5.36%)	31 (5.64%)	0.884	1.04(0.41-2.64); p=0.92	1.07(0.37-3.14); p=0.888
Comorbidity					
Hypertension, n (%)	46 (41.07%)	161 (29.27%)	0.014	1.27(0.81-1.99); p=0.278	1.25(0.65-2.40); p=0.486
Diabetes mellitus, n (%)	47 (41.9%6)	130 (23.64%)	<0.001	1.98(1.27-3.06); p=0.002	1.27(0.63-2.55); p=0.491
COPD, n (%)	15 (13.39%)	39 (7.09%)	0.026	1.79(0.94-3.44); p=0.075	1.80(0.80-4.08); p=0.154

Obesity, n (%)	44 (39.29%)	188 (34.18%)	0.336	1.31(0.83-2.04); p=0.235	2.06(0.83-5.11); p=0.117
Laboratory data					
HgbA1C % (mean ± SD)	6.26±1.85	5.70±1.4	<0.001	1.24(1.08-1.43); p=0.002	1.30(1.06-1.59); p=0.009
Total cholesterol (mean ± SD)	195.76±42.82	192.33±40.55	0.431	1.00(0.99-1.00); p=0.453	1.00(0.97-1.03); p=0.842
LDL cholesterol (mean ± SD)	122.06±34.39	116.82±37.1	0.182	1.00(0.99-1.00); p=0.166	1.00(0.97-1.03); p=0.631
HDL cholesterol (mean ± SD)	46.51±11.00	47.45±12.31	0.470	0.98(0.96-1.00); p=0.222	0.96(0.92-1.00); p=0.116
Triglycerides (mean ± SD)	136.60±67.65	136.34±88.10	0.976	1.00(0.99-1.00); p=0.924	0.99(0.98-1.00); p=0.521
Medications					
Aspirin, n (%)	21 (18.75%)	51 (9.27%)	0.003	1.62(0.90-2.92); p=0.103	1.00(0.47-2.57); p=0.826
ACE inhibitors, n (%)	14 (12.50%)	51 (9.27%)	0.295	1.23(0.65-2.33); p=0.521	0.92(0.34-1.97); p=0.672
ARBs n (%)	4 (3.57%)	24 (4.36%)	0.704	0.60(0.20-1.83); p=0.377	0.62(0.15-1.82); p=0.312
Statins n (%)	24 (21.43%)	84 (15.27%)	0.108	1.22(0.72-2.06); p=0.457	0.98(0.45-2.14); p=0.976

Table 3. Demographic and clinical characteristics of hospital-treated vs. COVID-19-positive patients.

Table 4. Demographic and clinical characteristics of dead vs surviving hospital-treated COVID-19-positive patients

	Dead **n= 7**	**Survived** **n= 105**	**p**	**Multiple logistic regression model adjusted for sex and age, OR (95% CI)**	**Multiple logistic regression model adjusted for sex, age, smoking status, medication use and comorbidities*, OR (95% CI)**
Age, years (mean ± SD)	80.71±20.51	61.72±13.50	0.0007	1.09 (1.03-1.16); p=0.005	1.09 (1.02-1.17); p=0.009
Sex (male), n (%)	3 (42.86%)	59 (56.19%)	0.49	1.03 (0.19-5.54) p=0.964	0.60 (0.06-5.67) p=0.657
Low-medium SES, n (%)	4 (57.14%)	76 (72.38%)	0.39	0.66 (0.12-3.61) p=0.635	0.76 (0.10-5.63) p=0.791
BMI, kg/m^2 (mean ± SD)	30.76±6.71	28.99±6.17	0.62	1.06 (0.85-1.32) p=0.564	1.09 (0.86-1.38) p=0.439
Currently smoking, n (%)	0	6 (5.71)	0.68	#	#
Comorbidity					
Hypertension, n (%)	3 (42.86%)	43 (40.95%)	0.92	0.51 (0.81-3.13) p=0.465	1.31 (0.13-12.63) p=0.337
Diabetes mellitus, n (%)	4 (57.14%)	44 (41.90%)	0.43	1.65 (0.29-9.34) p=0.571	3.19 (0.29-35.03) p=0.816
COPD, n (%)	1 (14.29%)	14 (13.33%)	0.94	0.68 (0.65-7.09) p=0.749	0.56 (0.02-16.06) p=0.343
Obesity, n (%)	1 (14.29%)	43 (40.95%)	0.68	0.72 (0.55-9.39) p=0.802	0.75(0.04; 12.49) p=0.739
Laboratory data					
HgbA1C % (mean ± SD)	7.11±2.01	6.37±1.75	0.29	1.23 (0.79-1.92) p=0.352	1.31 (0.75-2.32) p=0.276
Total cholesterol (mean ± SD)	162.48±42.96	197.79±42.73	0.0028	0.97 (0.95-0.99) p=0.046	0.91 (0.65-1.07) p=0.058
LDL cholesterol (mean ± SD)	100.33±20.93	123.38±34.67	0.11	0.97 (0.95-1.00) p=0.098	1.05 (0.76-1.47) p=0.762
HDL cholesterol (mean ± SD)	42.66±6.37	46.75±11.21	0.38	0.92 (0.83-1.03) p=0.166	1.09 (0.75-1.57) p=0.645
Triglycerides (mean ± SD)	115.03±79.43	137.90±67.12	0.42	1.00 (0.98-1.01) p=0.816	0.97 (0.89-1.05) p=0.441
Medications					
Aspirin, n (%)	1 (14.29%)	20 (19.05%)	0.75	0.38 (0.04-3.59) p=0.399	0.36 (0.02-6.85) p=0.514
ACE inhibitors n (%)	0	14 (13.33)	0.302	#	#
ARBs n (%)	0	4 (3.81)	0.591	#	#
Statins n (%)	1 (14.29)	23 (21.90)	0.449	0.35 (0.35-3.57) p=0.381	0.31 (0.01-6.57) p=0.449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Aspirin: NO
Age ranges
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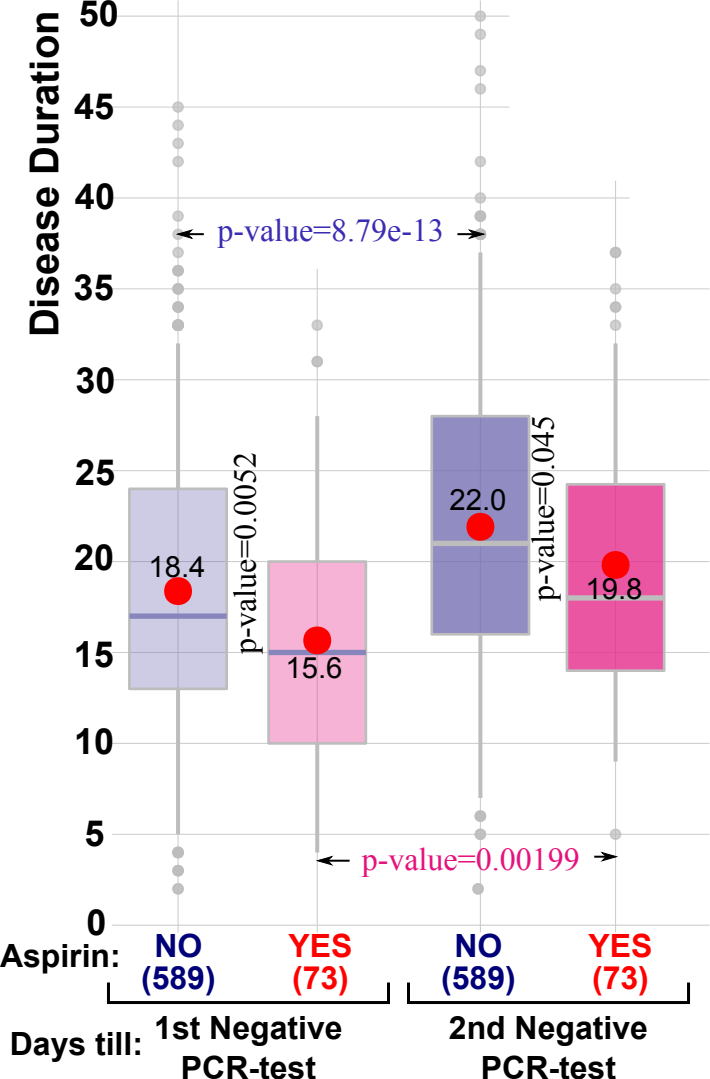
75-85
60-75
50-60
45-50
40-45
-6.7
-5.8
-6.5
-10.3
-6.4
15.6
-1.4
36.1
-0.8
20.7
-1.1
-44.9
Covid-19 density: positive > negative
Covid-19 density: negative > positive
-10
0
-40
-30
-20
-10
0
10
20
30
Δ density of aspirin
B
Aspirin | Statins: YES
Aspirin+Statins: NO
Age ranges
85+
75-85
60-75
50-60
45-50
40-45
-8.5
-3.9
-13.4
-3.3
-10.6
19.8
-4.8
39.5
-9.6
29.5
-0.1
-46.1
Covid-19 density: positive > negative
Covid-19 density: negative > positive
-10
0
-40
-30
-20
-10
0
10
20
30
40
Δ density of (aspirin, statins)


Disease Duration
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45
40
35
30
25
20
15
10
5
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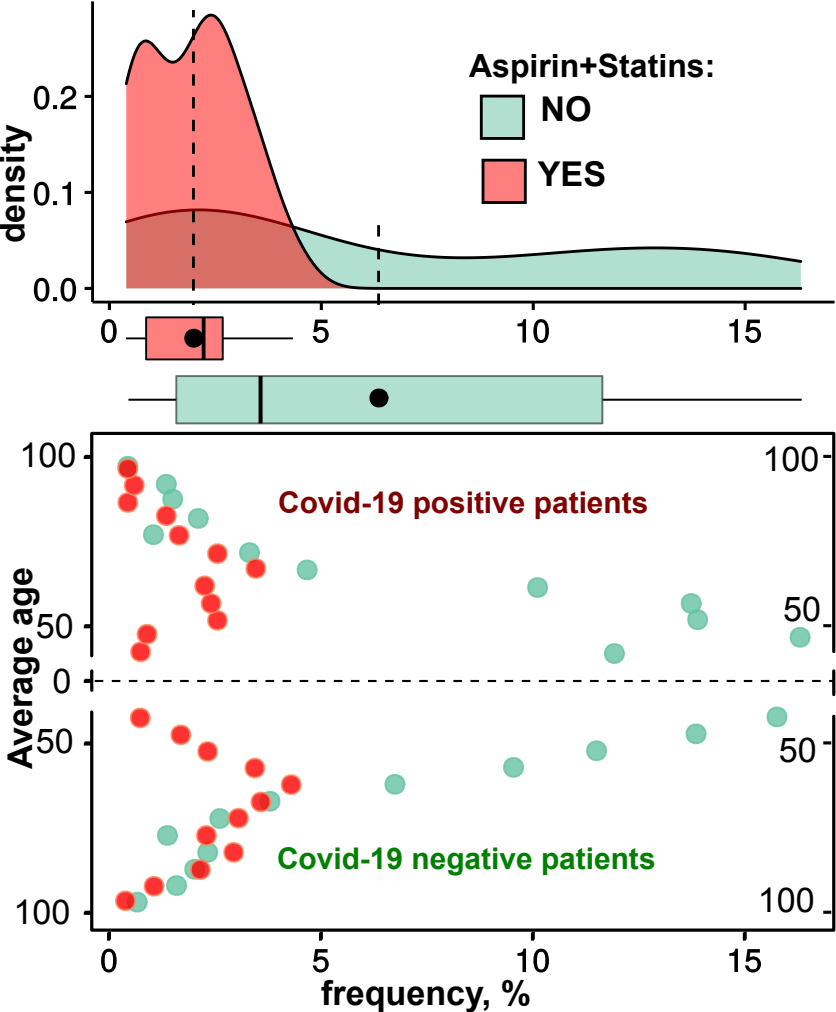
p-value=0.0052
p-value=0.045
p-value=0.00199
18.4
15.6
22.0
19.8
Aspirin:
NO (589)
YES (73)
NO (589)
YES (73)
Days till:
1st Negative PCR-test
2nd Negative PCR-test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0.1
0.0
Aspirin+Statins:
NO
YES
0
5
10
15
Average age
100
50
0
Covid-19 positive patients
Covid-19 negative patients
frequency, %